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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,149	03/02/2005	Anthony E. Bolton	355908-3303	2044

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FOLEY & LARDNER LLP
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EXAMINER

HADDAD, MAHER M

ART UNIT	PAPER NUMBER
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1644

MAIL DATE	DELIVERY MODE
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05/07/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/502,149

Applicant(s)

BOLTON ET AL.

Examiner

Maher M. Haddad

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 13-20 is/are pending in the application.
- 4a) Of the above claim(s) 13-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>11/12/04 & 11/26/04</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Notic to comply</u> . |

DETAILED ACTION

1. Claims 1-3 and 13-20 are pending.
2. Applicant's election without traverse of Group I, claims 1-3, directed to a composition of matter comprising bodies, wherein the bodies contain or are capable of expressing or expressible on the surface thereof an active group comprising the peptide sequence RGD filed on 2/26/07, is acknowledged.
3. Claims 13-20 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.
4. Claims 1-3 are under examination as they read on a composition of matter comprising bodies, wherein the bodies contain or are capable of expressing or expressible on the surface thereof an active group comprising the peptide sequence RGD.
5. Sequence compliance: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence.

Page 2, lines 16, and 19; page 2a, line 9; page 5, lines 4, 16 and 24; and page 6, lines 4, 11 and 20; page 7, lines 3, 6, 9, 14, 17 and 24; page 8, lines 6, 8, 11, 13, 15, 21, 23 and 25; page 11, line 3, and 20; page 12, line 6; page 14, lines 16 and 19; and page 15, line 16 have described the amino acid sequence RGDS that each must have a sequence identifier. Applicant is reminded of the sequence rules which require a submission for all sequences of 10 or more nucleotides or 4 or more amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

6. The specification is objected to for the following informalities:
 - a) the specification is objected to under 37 CFR 1.74 because it fails to provide "Brief Description of Drawings". When there are drawings, there shall be a brief description of the drawings. see MPEP 608.01(f).
 - b) page 5, line 20, the "patient's" and page 6, lines 8-11, the word "liposomes" "Forms" and "Approach" are misspelled.
 - c) page 6 shows the "20nm to about 1000nm, more preferably from about 50nm to about" in highlight. However, it is improper to use highlight in the specification.

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7. Applicant's IDS, filed 11/26/04 and 11/12/04, is acknowledged.

8. Claim 3 is objected to under 37CFR 1.821(d) for failing to recite the SEQ ID NO. in the claims.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

It is not clear that the skilled artisan could predict the efficacy of the RGDS-beads/-liposome on alteration of the cytokine profile of cells of mammalian immune system. The clinical value of such strategies remains to be seen. Finally, the specification does not provide empirical data to show the effect of RGDS-beads/-liposome on cytokine release.

The specification fails to provide sufficient guidance on how the claimed liposomes are capable of being phagocytosed by antigen-presenting cells. Liposome is a lipid bilayer that tends to fuse with the plasma membrane of target cell. Further, the specification fails to provide guidance on how the phagocytosed liposome/beads would result in the alteration of cytokine profile of cells of the mammalian immune system.

One cannot extrapolate the teachings of the specification to the scope of the claims because the alteration of cytokine profile are mutually exclusive function. The "alteration of cytokine profile" (promote or inhibit) are mutually exclusive activities in that they reach opposing endpoints, and that they employ structurally distinct *agonists* or *antagonists* to accomplish these mutually exclusive endpoints. Further, there is insufficient evidence or nexus that would lead the skilled artisan to predict the ability of the RGDS-beads or -liposomes to alter the cytokine profile.

While the Examiner acknowledged that the RGD motifs are well known in the art at the time of the invention, and RGD motifs are bound by surface integrin receptors. However, the

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specialized medical literature contains hundreds of reports indicating many RGD-related peptides with different activities and different efficacy. The use of peptides containing the RGD motif has been proposed in several pathologic conditions, with different activities including anti-angiogenesis, anti-thrombotic and anti-metastatic action. The specification does not provide guidance that an RGD motif with one activity can be used for another activity with the same efficacy. For example, the disintegrin kistrin which has amino acids flanking the RGD sequence (**PRGDM**P), is a potent inhibitor of platelet to fibrinogen but a poor antagonist of the binding of platelets to immobilized fibronectin (Lu X et al (1994) *Biochem J* 304: 929-936). In contrast, elegendin which has markedly different amino acids around RGD (**ARGDNP**), preferentially inhibited platelet adhesion to fibronectin as opposed to fibrinogen and binds to an allosterically distinct site on the α Ib β 3 complex.

It is unclear which patients would be candidates for in vivo treatment with anti-inflammatory RGDS-beads or -liposomes. For one to successfully use the RGDS-beads or -liposomes in vivo, which is suggested to work by targeting cell surface receptors, it is essential to understand what conditions are of interest to treat, if those molecules targeted participate in those conditions in vivo, what blocking intervention is most appropriate and the general criteria which will define quantitative endpoints for assessing efficacy. While the specification relies upon reducing the ear swelling in murine contact hypersensitivity (CHS) model with RGDS-beads as an assay for anti-inflammatory response (see Examples 2 and 3 of the instant specification); there is insufficient guidance and direction in the specification for diseases or conditions that would be targeted with such RGDS-beads. The specification does not teach how to extrapolate data obtained from *CHS* or *DHS* assays to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention.

Further, DTH and CHS do not provide the skilled artisan with guidance for how to use the claimed composition in vivo. The skilled artisan would conclude that a positive result in this assay indicates that the RGDS-beads composition is capable of inducing a hypersensitivity response, which is a non-specific response of the immune system to a substance recognized as toxic. Please see attached Barsoum et al. (1997, *Journal of Antimicrobial Chemotherapy* 40 :721-724) who induce a hypersensitivity response in mice in a similar way to that done in instant examples. In general, it is clear from the reference that such a response is not beneficial to the animal, as it indicates toxicity of the injected compound. This information does not guide the skilled artisan as to how to use the claimed composition. Thus, the skilled artisan would conclude that a positive result in this assay indicates that the RGDS-beads composition is capable of inhibiting a hypersensitivity response, which is a non-specific response of the immune system to a substance recognized as toxic. This information does not guide the skilled artisan as to how to use the claimed RGDS-beads composition in vivo to alter the cytokine profile. The ear swelling delayed-type hypersensitivity reaction (DTH) is not a model of a specific human disease, it is a standard test for examination of interventions impacting on the adaptive immune system in vivo. RGDS-beads composition administration inhibited the development of DTH in terms of cellular accumulation.

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Finally, the specification provides insufficient information as to the integrin receptor that is being targeted by the RGDS-beads composition on the dendritic cells (antigen-presenting cells). It is unclear what is the targeted integrin receptor that is present/expressed on the surface of the antigen-presenting cells would bind to the RGDS-beads and cause the dendritic cells to phagocytose the RGDS-beads which result in the alteration of the cytokine profile. The specification fails to show that the dendritic cells bind RGDS-beads.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

12. Claim 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Adderley and Fitzgerald (published 2000, IDS ref. C3).

Adderley and Fitzgerald teach a composition comprising streptavidin-coated Dynabeads ((M-280, 2.8- μ m diameter) within the claimed 20nm-500 μ m diametric dimension) coated with the amino-terminal-biotinylated peptide, b-RGDS in PBS (see page 5761, under *Coating of Streptavidin-coated Dynabeads with Biotinylated Peptides* in particular).

When a claim recites using an old composition or structure (e.g. RGDS-beads) and the use is directed to a result or property of that composition or structure (producing an anti-inflammatory response in vivo), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

While the prior art teachings may be silent as to the "the bodies are capable of being phagocytosed in vivo in a mammal by mammalian antigen-presenting cells resulting in the alteration of the cytokine profile of cells of the mammalian immune system and thereby

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producing an anti-inflammatory response in vivo in said mammal” per se; the product used in the Adderley and Fitzgerald reference is the same as the claimed product. Therefore, the intended use is considered inherent properties. In this case, Adderley and Fitzgerald teach the same composition as the claimed composition, the intended uses do not carry patentable weight per se and the claims read on the active or essential ingredients of the RGDS-beads composition. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Also, as restated in the court in Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

“Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. “The Court further held that “this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art”.

The reference teachings anticipate the claimed invention.

13. Claim 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Lestini et al (published 1/17/2002, IDS ref. C1).

Lestini et al teach a composition comprising a liposome wherein the liposome expressing on the surface an active group comprising the peptide RGD, the size of the liposome is 100 nm in diametric dimension (see page 238, under Preparation of RGD liposomes in particular). The intended use of the composition carry no patentable weight, and the composition read on the active or essential ingredient of RGD liposomes.

The reference teachings anticipate the claimed invention.

14. Claim 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/16202.

The WO '202 publication teaches a fusogenic liposome composition for delivering a liposome-entrapped compound into the cytoplasm of a target cell. The liposomes have an outer surface coating of unshielded (surface exposed) ligand effective to bind to specific cell surface receptors on the target cell membrane. The ligand molecules are carried on hydrophilic polymer chains which are anchored to the liposome by covalent attachment to a diacyl lipid. The hydrophilic polymer chains may be covalently attached to a liposome-bound lipid through a conventional bond such as irreversibly attached, or through a chemically releasable bond (see page 14, under section E. *Ligand Molecules*, in particular). Further, the '202 publication teaches RGD sequences of matrix protein as an example of ligands suitable for use in targeting the liposomes to specific cell types (see Table I, line 24 in particular).

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The reference teachings anticipate the claimed invention.

16. Claim 1-2 are rejected under 35 U.S.C. 102(e) as being anticipated by US. Pat. No. 7,060,291.

The '291 patent teaches and claims a liposome composition comprising a fusogenic liposome a linkeing moiety and a targeting moiety (see patented claim 1, in particular), wherein the targeting moiety is an RGD sequence (see patented claim 6 in particular). The '291 patent teaches that liposomes can have a variety of sizes, e.g., an average diameter as low as 25 nm or as high as 10,000 nm or more (see col., 5, lines 61-62 in particular).

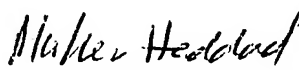
The reference teachings anticipate the claimed invention.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

April 17, 2007


Maher Haddad, Ph.D.
Primary Examiner
Technology Center 1600

Notice to Comply

Application No.

10/502,149

Applicant(s)

BOLTON ET AL.

Examiner

Maheer M. Haddad

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NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☒ 7. Other: The specification discloses the amino acid sequence RGDS without SEQ ID NO.

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

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